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DOI: https://doi.org/10.1159/000487431

Complementary Medicine Research
Practice | Methods | Perspectives

Research Report · Forschungsbericht

Complement Med Res 2018;25:269–273
DOI: 10.1159/000487431

Published online: June 22, 2018

Two Randomised Clinical Trials on the Use of *Bryophyllum pinnatum* in Preterm Labour: Results after Early Discontinuation

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Key Words
Bryophyllum pinnatum · *Kalanchoe pinnata* · Tocolysis · Nifedipine · Preterm labour

Schlüsselwörter
Bryophyllum pinnatum · *Kalanchoe pinnata* · Tokolyse · Nifedipin · Vorzeitige Wehen

Introduction

Preterm delivery is the most common cause of neonatal morbidity and mortality [1–3]. Since preterm contractions correlate highly with preterm delivery, their inhibition by tocolysis constitutes a major element in the corresponding treatment [4]. Beta-adrenergic receptor agonists, nifedipine and atosiban, are the main drugs for the pharmacological therapy of preterm contractions [4, 5].

The usage of *Bryophyllum pinnatum*, a herbal medication traditionally used in anthroposophic medicine, as a tocolytic was established in 1970 [6, 7]. Retrospective analyses revealed good effectiveness and very good tolerability in patients treated with *B. pinnatum* preparations [8, 9] and a matched-pairs study corroborated these results [10]. More recently, an observational study was performed [11]. The use of *B. pinnatum* as a tocolytic agent is supported by experimental evidence [12]. The available evidence demanded prospective, randomised trials to characterise efficacy. Here, 2 trials are described which were initiated independently to fill in this knowledge gap.

Patients and Methods

Both studies were approved by the local ethics committees (Trial I, Basel; Trial II, Zurich) and performed in accordance with the Declaration of Helsinki. All patients signed an informed consent form. In both trials, the number of recruited patients was markedly lower than the numbers determined in the power analysis; therefore, results are presented descriptively only. *B. pinnatum* preparations used in both trials were manufactured by Weleda AG, Arlesheim, Switzerland, according to Good Manufacturing Practice and with plant leaves provided by Weleda, Brazil (voucher specimen no. ZSS 29717 deposited at the Zurich Succulent Plant Collection, Switzerland). The preparations are registered in Switzerland without indication and are defined based on manufacturing procedures and specifications (mother tincture according to method 1.1.7. of the European Pharmacopoeia). Two classes of compounds from *B. pinnatum* leaves have so far been investigated in detail, the flavonoid glycosides and the bufadienolides [13].

Trial I (NCT00163579) was a prospective, randomised, double-blind, placebo-controlled, investigator-initiated clinical trial and started at Basel Women's University Hospital (UFK). The aim of the trial was to investigate the efficacy of *B. pinnatum* in the prophylaxis of preterm birth. The study was approved by Swiss Agency for therapeutic products (Swissmedic) and ran from February 2004 until April 2008. Women presenting with singleton pregnancies and at high risk of developing preterm contractions (e.g., prior preterm delivery, prior preterm contractions or prior cerclage) or with multiple pregnancies were recruited, if they did not fulfil the following exclusion criteria: age under 18 years, Body Mass Index ≥ 30, foetal malformations known at the time of recruitment and intrauterine growth restriction. The randomisation of the 2 groups was performed using program Z by the hospital pharmacy and took place after the 26th gestational week. Study medication was *B. pinnatum* 33% tincture (33% of fresh plant with 45% ethanol w/w; final ethanol content 36% v/v; DEV 0.04:1, i.e., 40 mg dried *B. pinnatum* matter in 1 g mother tincture). The hospital pharmacy of the University Hospital Basel produced the placebo solution (1% ferric chloride solution, similar mixture of ethanol and water). Pregnant women received 20 drops 5 times a day of either *B. pinnatum* tincture 33% or placebo (i.e., maximal ethanol doses per day 0.96 g). In the cases in

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Table 1. Baseline characteristics and outcomes of the pregnant women (n = 26) participating in Trial I and treated with *B. pinnatum* or placebo[a,b]

	B. pinnatum			Placebo		
	Singletons (n = 8)	Multiples[c] (n = 5)	Total (n = 13)	Singletons (n = 5)	Multiples[d] (n = 8)	Total (n = 13)
Age, years	30.6 ± 5.2	30.8 ± 3.6	30.7 ± 4.5	26.8 ± 6.1	29.8 ± 4.0	28.6 ± 4.9
Nicotine, n						
Yes	2	0	2	0	0	0
No	6	5	11	4	8	12
Parity, n						
0	5	4	9	4	6	10
1	3	1	4	1	2	3
Gravidity, n						
1	4	3	7	3	5	8
2	3	1	4	0	1	1
≥ 3	1	1	2	2	2	4
Hospitalisation, n	8	5	13	5	8	13
Additional Tocolysis, n	8	5	13	5	8	13
Lung maturation, n						
Yes	7	4	11	5	7	12
No	0	1	1	0	0	0
Unknown	1	0	1	0	1	1
Gestational age at study begin, weeks	30.3 ± 1.5	24.1 ± 4.4	27.9 ± 4.2	30.8 ± 1.1	26.5 ± 3.3	28.2 ± 3.4
Vaginal infection, n	4	1	5	4	3	7
Gestational age at study end, weeks	32.8 ± 1.4	32.1 ± 6.1	32.6 ± 3.1	34.6 ± 2.4	29.8 ± 5.1	31.6 ± 4.8
Treatment duration, days	18.7 ± 9.07	50.3 ± 14.6	28.2 ± 18.3	22.5 ± 3.5	24.2 ± 10.8	23.7 ± 9.0
Gestational age at delivery, weeks	36.3 ± 2.7	31.3 ± 3.9	34.4 ± 4.0	38.2 ± 2.2	31.9 ± 4.1	34.3 ± 4.6
Delivery, n						
Vaginal	7	0	7	5	7	12
Caesarean	1	5	6	0	1	1
Preterm delivery, n	4	5	9	1	7	8
Term delivery, n	4	0	4	4	1	5
Compliance, n						
Good	7	3	10	2	5	7
Partial	1	0	1	1	1	2
Unknown	0	2	2	2	2	4
Hospitalisation, days	13.5 ± 9.8	31.0 ± 24.0	20.2 ± 18.1	10.6 ± 13.6	21.1 ± 18.1	17.1 ± 16.8
Newborns' weight, g	2736 ± 597	1481 ± 785	1538± 767	3206 ± 544	1828 ± 786	1721 ± 678
Newborns' length, cm	47.1 ± 2.7	39.6 ± 4.6	39.7 ± 5.1	49.4 ± 1.8	43.1 ± 6.1	40.1 ± 6.2
pH arterial umbilical blood	7.25 ± 0.15	7.36 ± 0.03	7.31 ±0.01	7.25 ± 0.10	7.31 ± 0.04	7.30 ± 0.05
pH venous umbilical cord	7.36 ± 0.09	7.38 ± 0.03	7.34 ± 0.05	7.31 ± 0.11	7.37 ± 0.04	7.34 ± 0.4
Apgar score 5 min	9.4 ± 1.06	7.0 ± 2.7	8.5 ± 0.7	9.4 ± 1.34	8.3 ± 2.4	8.6 ± 1.1
NICU	0	1 (triplets)	1 (triplets)	0	3	3

[a]Data are shown either as mean ± standard deviation or as number of patients.
[b]Missing values *B. pinnatum group* (placebo group) for gestational age at study end, n = 1 (n = 1) in the singleton subgroup and n = 2 (n = 1) in the multiple subgroup. Missing values for treatment duration or values excluded due to low compliance in the *B. pinnatum* group (and placebo group): singleton subgroup n = 1 (n = 3), multiple group n = 2 (n = 3).
[c]twins, n = 3; triplets, n = 2.
[d]twins, n = 8.
NICU = neonatal intensive care unit.

which these treatments were not efficiently preventing preterm painful contractions (no additional criterion), participants received standard tocolysis with or without lung maturation. The main outcome was pregnancy duration. The power was calculated to be approximately 80% with a detectable difference of ≥10 days and a sample size of 30 (per group, for each of the 3 initial hypotheses) with a standard deviation of 2 weeks.

Trial II (NCT00391339 [14]) was a prospective, controlled, open-labelled randomised, clinical trial initiated at the University Hospital Zurich and sponsored by Weleda AG. The aim of this study with a parallel design was to compare efficacy and safety of *B. pinnatum* 50% tablets and nifedipine in tocolysis. All study documents were approved by Swissmedic. The study ran from December 2006 until November 2009. In- and outpatients were included based on the following criteria: single pregnancy, gestational age < 34 weeks and 1 day, indication for loading treatment with nifedipine due to premature labour, Bishop score < 5, negative fibronectin test, lack of vaginal bleeding, no contraindication for nifedipine or *B. pinnatum*, no drug abuse, no participation in another trial in the last 4 weeks. Study medication was *B. pinnatum* 50% as chewable tablets (each 350 mg tablet corresponds to 170 mg of leave press juice, dried down to 17 mg by mixing with lactose; 100 mg dried *B. pinnatum* matter in 1 g). Nifedipine, a standard medication at the University Hospital Zurich,

Table 2. Trial II: Outcomes in patient groups treated with *B. pinnatum* or nifedipine at different examination time points (including baseline)[a]

	B. pinnatum[b] (n = 14)	Nifedipine[c] (n = 13)
Baseline		
Gestational age, weeks	29.4 ± 3.2	27.8 ± 3.8
CTG, contractions/h	9.6 ± 5.6	7.7 ± 5.9
Bishop score	2.1 ± 1.2	1.4 ± 1.3
Haematological parameters		
Leucocytes, 1E3/µl	11.7 ± 2.5	10.8 ± 2.6
Thrombocytes, 1E3/µl	278 ± 59	251 ± 35
AST, U/l	19.7 ± 4.9	23.9 ± 4.3
ALT, U/l	18.9 ± 12.9	16.7 ± 6.5
CRP, mg/l	5.3 ± 4.8	10.1 ± 11.8
BPS, mm Hg	110 ± 10	111 ± 14
BPD, mm Hg	59 ± 11	63 ± 11
Pulse, bpm	79 ± 8	81 ± 14
At 0–1h		
BPS, mm Hg	108 ± 11	104 ± 8
BPD, mm Hg	66 ± 12	58 ± 12
Pulse, bpm	80 ± 11	89 ± 13
At 4h		
CTG, contractions/h	4.5 ± 4.2	3.8 ± 3.2
Bishop Score	2.1 ± 1.3	1.3 ± 0.8
BPS, mm Hg	111 ± 9	111 ± 16
BPD, mm Hg	66 ± 8	66 ± 17
Pulse, bpm	78 ± 14	87 ± 8
Adverse reactions, yes/no	0	6
Headache[d]	0	6
Dizziness[d]	0	2
Vomiting[d]	0	1
Study stop[d]	0	1
At 49h		
Haematological parameters		
Leucocytes, 1E3/µl	12.2 ± 3.3	11.1 ± 3.8
Thrombocytes, 1E3/µl	271 ± 54	253 ± 39
AST, U/l	20.9 ± 8.3	22.3 ± 4.9
ALT, U/l	19.1 ± 10.2	16.2 ± 5.6
CRP, mg/l	6.6 ± 5.2	8.4 ± 4.1
BPS, mm Hg	108 ± 12	107 ± 9
BPD, mm Hg	62 ± 11	63 ± 4
Pulse, bpm	85 ± 15	82 ± 8
Tocolysis after 49h		
Yes	12	11
No	1	1
Puerperium		
Gestational age at delivery, weeks	38.7 ± 2.1	37.4 ± 1.7
BPS, mm Hg	115 ± 8	110 ± 11
BPD, mm Hg	70 ± 8	64 ± 13
Pulse, bpm	73 ± 14.9	76 ± 10.9
Hospitalisation antepartum, days	9.4 ± 9.7	10.4 ± 20.5
Hospitalisation postpartum, days	4.6 ± 1.3	5.6± 1.2
Newborns' weight, g	3246 ± 580	2957 ± 478
Newborns' height, cm	49.3 ± 2.6	48.0 ± 2.8
Apgar		
1'	8.0 ± 1.0	8.2 ± 0.9
5'	9.1 ± 0.7	9.1 ± 0.7
10'	9.3 ± 0.5	9.3 ± 0.5

[a]Data are shown either as mean ± standard deviation or as number of patients.
[b]Missing values B. pinnatum group: pulse at baseline examination, n = 3; blood pressure systolic and diastolic at 3rd examination, n = 1; pulse at 3rd examination, n = 2.
[c]Missing values nifedipine group: blood pressure at baseline examination, n = 1; pulse at baseline examination, n = 2; pulse and blood pressure at 1st examination, n = 1; CTG, Bishop score and adverse reactions at 2nd examination, n = 1; pulse and blood pressure at 2nd examination, n = 2; haematological parameters at 3rd examination, n = 1; pulse and blood pressure at 3rd examination, n = 2; all values at the 4th examination, n = 1.
[d]Several reactions possible.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; bpm = beats per minute; BPS = blood pressure systolic; BPD = blood pressure diastolic; CRP = C-reactive protein; CTG = cardiotocography.

was available as Nifedipin Mepha® 10 mg capsules (Mepha Pharma AG, Aesch, Switzerland) and Adalat CR® 30 mg and 60 mg tablets (Bayer AG, Zurich, Switzerland). The hospital pharmacy managed the randomisation of the *B. pinnatum* and nifedipine groups with the program Randlist Version 1.0 (Datinf GmbH, Tuebingen, Germany). Patients in the *B. pinnatum* group were treated with 1 chewable tablet every 15 min during the first treatment hour, followed by 2 chewable tablets every 6 h. Patients in the nifedipine group were given one Nifedipin Mepha® 10 mg capsule every 15 min during the first treatment hour. After 1 h and 15 min, they were given an Adalat CR® 60 mg tablet. Afterwards, patients received an Adalat CR® 60 mg or Adalat CR® 30 mg tablet alternately every 12 h over the following 48 h. The main outcome was the difference in patients' response to tocolysis (contraction frequency had decreased, or contraction frequency had not decreased, but the Bishop score was <5) between the 2 groups. For this one-sided equivalence test, results for the main outcome parameter with power 90% and significance level alpha = 0.05 lead to an estimated number of required 69 patients per study group. Thereby, a success rate of nifedipine of 80% and a detectable minimum success rate of 60% in the *B. pinnatum* group were assumed. Because of possible dropouts, the effectively required number of patients was increased to 70 per group.

Results

Trial I

For this section, see table 1. At study discontinuation, 26 pregnant women had been recruited. Duration of pregnancy was comparable in the groups with and without *B. pinnatum.* All patients were hospitalised and received additional tocolysis (atosiban, hexoprenalin, indomethacine, nifedipine and oral magnesium salt); one patient of the *B. pinnatum* group was additionally given progesterone. In the *B. pinnatum* group, most patients were treated with hexoprenalin and nifedipine (5/13), with hexoprenalin alone (3/13) or with nifedipine alone (2/13). In the placebo group, most patients were treated with hexoprenalin alone (8/13) or with atosiban (2/13). No serious adverse drug reactions occurred during this study. In the *B. pinnatum* group, 1 newborn had a pathological genetic analysis (Factor V Leiden thrombophilia); no perinatal deaths occurred.

Trial II

For this section, see table 2. The study was stopped prematurely when 27 patients had been recruited. Both groups were comparable at baseline, except that patients of the *B. pinnatum* group were on average 2 years older at recruitment than patients from the nifedipine group (32.9 vs. 30.9 years). A comparable decrease in contraction frequency from the baseline examination to the examination after 4 h of treatment was observed in the 2 groups. The tolerability of the therapy was documented after 4 h as very good in 9 cases of the *B. pinnatum* group (good: n = 5; moderate: n = 0) and in 1 case of the nifedipine group (good: n = 8; moderate: n = 3). In addition, after 49 h the tolerability was also very good in 9 cases of the *B. pinnatum* group (good: n = 5) and in 1 case of the nifedipine group (good: n = 8; moderate: n = 2; poor: n = 1). Alanine aminotransferase, aspartate aminotransferase and C-reactive protein values were comparable in the various examinations and in the 2 groups. No serious adverse events happened during the study.

Discussion

In the last decade, *B. pinnatum* began to be used at university institutions in Switzerland, where at present it constitutes an inherent part of the standard preterm contractions treatment (see [15]). The relatively low evidence level on which this use of *B. pinnatum* is based, together with the lack of fully efficacious and well-tolerated synthetic, tocolytic agents, makes the performance of randomised controlled trials urgent. Given the low number of patients who could be recruited in the 2 trials described here, no definitive conclusions on efficacy and safety are possible, although some results are promising for subsequent studies. This manuscript should be seen mainly as a contribution to bias reduction in clinical research.

Poor recruitment rate is the most common reason for trial discontinuation [16, 17] and should be reported and discussed. In the case of the present studies, the difficulties inherent in carrying out clinical trials with pregnant women are likely to have contributed to the severe delay in patient recruitment. The previous use of *B. pinnatum* preparations by several screened patients at study initiation might have played a role, as well as the low budgets. Although trials I and II reveal the willingness of Swiss university institutions to investigate promising herbal products, the faced difficulties must be avoided in the future. For this purpose, enhanced financial and human resources for future randomised clinical trials are urgently needed.

Disclosure Statement

M.S. and M.M. are employees of Weleda AG, the company that produces the preparations of *Bryophyllum pinnatum* used in both trials. A.P.S.-W. and U.M. received research funding from Weleda AG during the last 5 years.

Acknowledgments

We thank all professionals at the Basel Women's University Hospital and at the Obstetrics Department from the University Hospital Zurich, who facilitated Trials I and II, especially Prof. Dr. R. Zimmermann (USZ). We are indebted to all actual and past members of the *Bryophyllum* study group who contributed to the present work, in particular to Dr. M. Ramos. Dr. H. Murray is gratefully acknowledged for language corrections. Weleda AG provided the study preparation for Trial I and sponsored Trial II.

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